Therapy of Acute Hepatitis B

Jay H. Hoofnagle, M.D.
Director, Liver Diseases Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

The incidence of acute hepatitis B has been declining in the United States for the past 15 years, largely as a result of increasing use of HBV vaccination.[1] As a consequence, the overall incidence of reported acute hepatitis B has declined by 75%, with the greatest decreases occurring in children. Unfortunately, cases of acute hepatitis B still occur and account for ~ one-third of acute viral hepatitis in the United States. Furthermore, fulminant hepatitis B remains an important problem and is the reason for ~ 1% of liver transplants done in adults each year. Clearly, recommendations for HBV vaccine in the United States have had major effects on the incidence of this disease, but gaps in its application persist, and further efforts to expand vaccine use are warranted. Every case of acute hepatitis B represents a failure of preventive medical care.

The course and outcome of acute hepatitis B varies greatly by age and sex. At least 90% of newborns, but only 30% of infants and fewer than 10% of adults with HBV, develop chronic infection. Among adults, men who are acutely infected are more likely to develop chronic hepatitis B than women. Symptoms and jaundice have the opposite associations with age and sex from chronicity. Newborns and infants rarely experience jaundice or symptoms during acute hepatitis B, compared to at least 40% of adults.[2] Furthermore, patients who develop jaundice and symptoms are the least likely to develop chronic infection. Indeed, the majority of patients with chronic hepatitis B deny a clinical history of acute hepatitis or jaundice, and most large series of cases of acute, icteric hepatitis B have included few if any patients who developed chronic infection.

Several antiviral therapies and strategies have been used in acute hepatitis B, but none has been shown to be beneficial or to alter the course and outcome of the infection. Therapies that have been approved for chronic hepatitis B—alpha interferon, peginterferon, lamivudine, adefovir dipivoxil, and entecavir—have not been applied to large numbers of cases of acute disease and none, except for standard alpha interferon, has been subjected to a prospective, randomized controlled trial.

While most patients with acute hepatitis B recover spontaneously without residual liver damage, therapy can be justified for several reasons, and each deserves comment:

- To prevent fulminant hepatitis and death
- To prevent evolution to chronic infection
- To shorten the course of disease and ameliorate symptoms

Fulminant hepatitis is rare, but eventuates in 1 to 2% of adults with acute icteric hepatitis B and is still an important reason for liver transplantation in the United States and the Western world. Antiviral therapy is often given to patients with severe hepatitis B, but the evidence of benefit is sparse. Small case series on use of alpha interferon in

fulminant hepatitis B have suggested little benefit and side effects (fever, neutropenia, thrombocytopenia) may complicate the course of disease. Promising results have been reported on the use of lamivudine in fulminant or severe hepatitis B in several small case series[3-5] and a modest sized study from Germany[6] in which 82% of 17 patients with severe hepatitis B (INR > 2) given lamivudine survived, compared to only 20% of 20 untreated, historic controls. The difficulty with interpreting these results, however, was that the criteria for fulminant hepatitis (hepatic encephalopathy) was not met by most patients in these series, and the high rate of recovery may have reflected treatment of severe rather than fulminant disease. Nevertheless, an argument can be made for routine use of lamivudine in patients with fulminant hepatitis B, since many such patients will ultimately require liver transplantation and early institution of antiviral therapy is appropriate to attempt to prevent recurrence of the infection in the allograft. The excellent safety record of lamivudine and lack of adverse events in reported series on fulminant hepatitis supports this recommendation.

Chronic hepatitis eventuates in up to 10% of adults with acute hepatitis B. However, most patients with chronic hepatitis have anicteric and asymptomatic acute infection, and chronicity from acute, icteric disease is rare. In a prospective, randomized controlled trial of alpha interferon in 100 patients with acute hepatitis B from Greece, patients with acute symptomatic hepatitis B were given either 3 or 10 million units of interferon alfa-2b or placebo three times weekly for 3 weeks.[7] In followup, all patients in all three groups recovered and cleared HBV DNA and HBsAg. Thus, prevention of chronicity, which is used as a rationale to treat acute hepatitis C, does not justify use of antiviral therapy in acute hepatitis B because the majority of patients recover completely.

Shortening the course of illness and ameliorating symptoms is a more restricted but nevertheless potentially valuable rationale for therapy of acute hepatitis B. While almost all patients with acute, icteric hepatitis B recover, the illness can be prolonged and temporarily disabling. However, the evidence that antiviral therapy ameliorates the course of illness is sparse. Perhaps one exception to this is the potential amelioration of protracted, severe hepatitis B. Indeed, examples presented in the majority of case series of hepatitis B have more likely represented protracted rather than fulminant illness. The excellent tolerance and safety of lamivudine (and lack of chronicity in reported series) argues for the use of this agent in severe and protracted cases. The difficulties with this approach, however, are that it has not been proven to be beneficial, and the definition of "protracted, severe" disease is vague. Furthermore, one must be careful to distinguish between protracted acute hepatitis B and a severe reactivation of chronic hepatitis B.

Needs for the future. It is unlikely that randomized controlled trials of antiviral therapy will be conducted in either typical or fulminant acute hepatitis B: the disease is too uncommon, and the logistics for establishing such studies are enormous. Regardless, it is appropriate to establish a definition for protracted, severe hepatitis B that might encourage clinical trials or at least a comparison of results of antiviral therapies against historic controls. A tentative definition might be: a patient with HBsAg, IgM anti-HBc, and HBV DNA (perhaps > 10,000 IU/ml) in serum for at least 4 weeks after onset of symptoms accompanied by elevations in serum bilirubin (perhaps > 10 mg/dl) and

prothrombin time (perhaps INR >1.5) but without hepatic encephalopathy. In the interim, antiviral therapy with nucleoside analogues is appropriate for fulminant hepatitis B but is not warranted in typical, uncomplicated cases of acute hepatitis B.

References

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